EPA-540/1-86-025

Office of Emergency and
Remedial Response
Washington DC 20460

Office of Research and Development
Office of Health and Environmental
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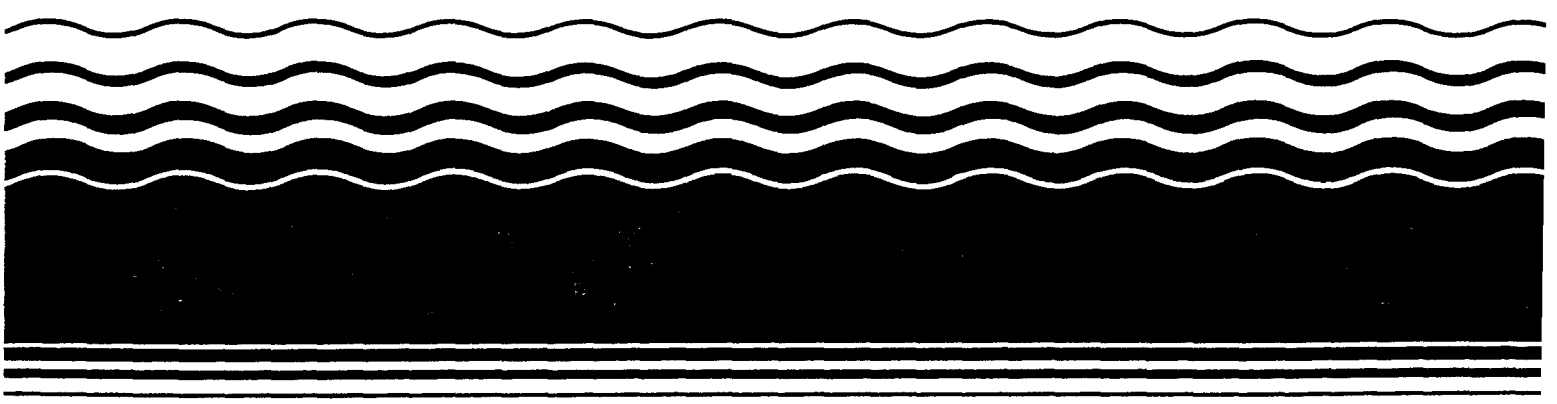
HEALTH EFFECTS ASSESSMENT FOR COPPER



EPA/540/1-86-025
September 1984

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U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
Washington, DC 20460

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This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with copper. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) source has been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Copper. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-036. NTIS PB 81-117475. (Cited in U.S. EPA, 1985)

U.S. EPA. 1983a. Technical Support Document on the Ranking of Hazardous Chemicals Based on Carcinogenicity. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985. Drinking Water Criteria Document on Copper. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH OHEA for the Office of Drinking Water, Washington, DC. Final Draft.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983b).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates.

Copper is an essential trace element. In individuals with normal copper metabolism and normal levels of G6PD, there seems to be a wide separation between required levels and toxic levels. The present document reflects the estimate of 2.6 mg/day for both the AIS and AIC. This is the daily exposure level suggested by U.S. EPA (1985) and is based on human GI symptoms following acute exposure. This value is also in good agreement with the limited animal data. A CS of 19 was estimated for elevated serum AST activity and jaundice in pigs fed high levels of copper sulfate.

No good quantitative animal data exist for inhalation exposure and effects of copper. For this reason the TLV values, 0.2 mg/m^3 for fumes and 1.0 mg/m^3 for dusts and mists, were used to estimate inhalation AICs. The ACGIH (1983) based these levels on extensive industrial experience with copper in Great Britain. The estimated AICs are: 0.14 mg copper vapor/day; 0.71 mg copper mist or dust/day. These suggestions should be reviewed as more complete data become available.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

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ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
AST	Aspartate transaminase
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstracts Service
CS	Composite score
CNS	Central nervous system
DNA	Deoxyribonucleic acid
GI	Gastrointestinal
GRAS	Generally regarded as safe
G6PD	Glucose-6-phosphate dehydrogenase
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RV_d	Dose-rating value
RV_e	Effect-rating value
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Copper is a metal belonging to the First Transitional Series of the periodic table. Elemental copper has a CAS number of 7440-50-8. Copper occurs in nature as the elemental metal (zero valence), and in the +1 and +2 valence states. In addition to a variety of inorganic compounds, copper forms a number of compounds with organic ligands. Both organic and inorganic copper compounds have a variety of uses (Kust, 1979). Most Cu^{+1} compounds are not stable in the environment, particularly in the presence of water or moisture and air, and tend to change to the stable Cu^{+2} state (Kust, 1979).

In the atmosphere, copper is present as dusts and fumes from copper smelting industries, iron and steel industries, coal burning power plants and other miscellaneous fabricating operations involving copper (NAS, 1977). The atmospheric fate of copper has not been studied comprehensively. Any chemical interaction of copper compounds in the atmosphere is likely to result in speciation (i.e., conversion of copper compounds into a stable species such as CuO), not in its direct removal through decomposition as frequently occurs with organic compounds. The principal removal mechanisms for atmospheric copper are probably wet and dry deposition. The atmospheric half-life for the physical removal mechanism is expected to depend on the particle size and particle density of atmospheric copper. No estimate for the atmospheric half-life of copper is available.

The aquatic fate of copper has been studied more extensively than its atmospheric fate (Callahan et al., 1979). The two processes that are likely to dominate the fate of copper in aquatic media are chemical speciation and sorption (Callahan et al., 1979). The nature of chemical speciation of copper in aquatic media is determined by the oxidation-reduction potential

of the particular copper compound and the pH of the aquatic media. In aquatic media of pH <7, copper may exist in Cu^{+2} form, whereas at pH >7, copper may exist as the carbonate complex. In polluted water bodies, copper may form complexes with organic material in the water. Various sorption processes reduce the level of ionic state carbonate complex or organic complex of copper from aquatic media. Sorption onto clay materials, hydrous iron, manganese oxides and organic material is the primary controlling factor (Callahan et al., 1979). In organically rich sediments, the sorbed and precipitated copper may become redissolved through complexation and may persist in the water for a long time. No estimate of the aquatic half-life of copper is available in the literature.

The fate of copper in soil has been studied inadequately; however, the fate may depend upon the pH of the soil, its moisture content and its clay and organic matter content (NAS, 1977). In acidic soils, copper may be more soluble, which would enhance its mobility (NAS, 1977); the reverse may be true in basic soils. Soils rich in organic matter may enhance the mobility of copper through complexation. Both clay and organic matter may facilitate the sorption of copper in soil, however, and may retard its leachability. Soils with suitable moisture content may enhance the microorganism activity and the partial removal of copper through uptake by microorganisms. No estimate of the half-life of copper in soils is available; however, copper is expected to be leached more readily from acidic and sandy soils than from basic soils containing a higher percentage of clay and/or organic matter.

The BCFs for copper in aquatic organisms have been determined by several investigators and have been found to vary from 12 for an alga, Scenedesmus quadricarda, to 30,000 for molluscs (Callahan et al., 1979).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

According to Schroeder et al. (1966), humans ingest an average of 2.5-5 mg of copper/day from dietary sources. These authors estimated that GI absorption of ~3.2 and 0.2 mg of copper occurs from food and fluid intake, respectively. The actual quantities of copper absorbed depend on geography, climate, soil chemistry, diet, water softness and pH.

Weber et al. (1969) administered ^{64}Cu as copper acetate to seven fasted human subjects without liver damage. Because of the short half-life of ^{64}Cu (12.8 hours), labeled (^{95}Zr) zirconium oxalate was given as a non-absorbable stool marker to enable location of the copper acetate bolus. The radionuclides were counted daily for 4 days in a whole body scintillation counter, and GI movement of the administered bolus was monitored with a scintillation camera. Radioactive copper in blood was determined hourly for 6 hours and in urine and stools daily.

Absorption of ^{64}Cu appeared to be diphasic. Maximum absorption from the stomach and duodenum occurred within 1 hour of administration. A second and slower absorption phase was observed >3.5 hours post-administration. At 2 hours post-administration the ^{64}Cu acetate bolus had left the stomach of the subjects and was located in the small intestine; 3 hours later it was located in the terminal ileocecal region and proximal large intestine. Average net absorption of ^{64}Cu was ~60%, with a range of 15-97% (Weber et al., 1969). Evans (1973) stated that, in mammals, alimentary absorption of copper occurs only from the upper GI tract and that the extent of absorption may be influenced by competition of other metals for metallothionein binding sites (necessary for active transport of copper), levels of dietary protein, kinds and amounts of anions present and the level of dietary ascorbic acid.

2.2. INHALATION

Quantitative data regarding absorption of copper from inhalation exposure could not be located in the available literature; however, presumptive evidence has been located. Villar (1974) observed copper-containing granulomas in the lung, liver and kidney upon necropsy of an individual occupationally exposed to Bordeaux mixture (an aqueous solution of lime and 1-2% copper sulfate) used in spraying vineyards. Pimental and Menezes (1975) noted copper-containing liver granulomas in three patients who had used Bordeaux mixture while spraying vineyards to prevent mildew. Gleason (1968) reported symptoms of "metal fume fever" (general discomfort, fever, chills, stuffiness of the head) in three workers exposed to fine copper dust at concentrations of 0.03-0.12 mg/m^3. Installation of an exhaust fan that reduced air levels to <0.008 mg/m^3 promptly alleviated these symptoms.

Batsura (1969) exposed rats (strain, sex and number not specified) for 15, 30, 45, 60 or 180 minutes to 50-80 mg copper oxide/m^3. Electron microscopy showed that copper absorption had occurred in rats exposed for 180 minutes. Copper oxide particles had penetrated the epithelial cells of the pulmonary alveoli and were found in plasma 6 hours after exposure began. Particles were also found in the proximal convoluted tubules of the kidney.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral Exposure. There are a number of acute/subchronic case reports of accidental human exposure. Only those which provided data sufficient to estimate exposure levels are summarized here.

Chattani et al. (1965) evaluated clinical data from 53 patients who ingested copper sulfate in suicide attempts. The amounts of copper ingested ranged from 0.25-7.6 g of copper. Five patients died and the survivors exhibited a variety of symptoms most prevalent of which were nausea, vomiting and epigastric pain.

Semple et al. (1960) reported an outbreak of gastroenteritis affecting 18/50 workmen following ingestion of copper sulfate contaminated water. Symptoms included dizziness, headache, diarrhea, vomiting and abdominal pain. Later analysis of the water source showed copper levels of $\geq$44 ppm. Assuming each man drank 1 cup (0.23 ℓ) the estimated dose was 0.143 mg/kg copper (U.S. EPA, 1985).

Nicholas and Brist (1968) reported a similar incidence. In this case 9/20 had diarrhea, 6/20 vomiting and 9/20 nausea. A sample of tea showed 30 ppm copper. U.S. EPA (1985) estimated the dose was >0.1 mg/kg.

Wyllie (1957) reported an outbreak of copper poisoning due to copper leaching from a cocktail shaker. Amounts of copper ingested were estimated to be 5.3-32 mg copper. Of the women exposed 10/15 reported symptoms including weakness, abdominal cramps, headaches, nausea, dizziness and vomiting.

Little information exists concerning subchronic toxicity of copper in the usual laboratory species. Howell (1959) maintained rats on diets containing 5000 ppm copper acetate for 16 months. Assuming that rats consume

food equivalent to 5% of their bw/day, these rats consumed ~250 mg copper acetate or ~80 mg Cu/kg bw/day. No criteria of toxicity were mentioned. Liver and kidney were found to accumulate copper heavily, but no accumulation was found in the cornea or brain.

Dietary levels of ~200 ppm copper have long been used as growth promoters in the production of market hogs. Kline et al. (1971) exposed groups of 12 Hampshire and Yorkshire pigs weighing an average of 22.2 kg to dietary levels of 0, 150, 200 or 250 ppm copper sulfate for 88 days (Table 3-1). Accelerated rate of weight gain and elevated levels of liver copper were demonstrated at all treatment levels. Hepatic copper levels linearly ($p<0.05$) correlated with dose. Depressed growth rate and blood hemoglobin concentration were observed in pigs fed a diet containing 500 ppm copper sulfate for 61 days.

Suttle and Mills (1966a) added 750 ppm of basic copper carbonate ($CuCO_3 \cdot Cu(OH)_2 \cdot H_2O$) to the cornmeal diets of weanling female Large White pigs, alone or with supplemental zinc (500 ppm $ZnCO_3$) or iron (750 ppm $FeSO_4 \cdot 7H_2O$) in separate experiments. Six pigs per test group were maintained on the diets for 42 days (zinc experiment) or 49 days (iron experiment), and the daily doses in both experiments (calculated from food consumption and average weight data) were ~22 mg Cu^{2+}/kg bw/day. Addition of copper to the diet at this level was toxic to 9 of the 12 control (copper without zinc or iron) pigs, as evidenced by 2- to 5-fold increases in serum copper and AST, and jaundice (7 pigs). These effects were most severe after 4 weeks but returned to normal after 6 weeks, suggesting adaption; but growth depression, reduced food conversion efficiency (food consumed/live weight gain) and reduced hemoglobin (microcytic hypochromic anemia) were also observed and persisted throughout the exposures. It

TABLE 3-1

Effects of Copper Sulfate·$5H_2O$ Administered in Corn-Soy Diet*

Species/Strain	Sex/No.	Average Body Weight (kg)	Dose	Duration (days)	Effects
Pig/Hampshire and Yorkshire	NR/8	23.6	250 ppm diet 3.2 mg Cu^{+2}/kg/day	61	accelerated growth with less feed
Pig/Hampshire and Yorkshire	NR/8	23.6	500 ppm diet 5.5 mg Cu^{+2}/kg/day	61	reduced growth and hemoglobin levels, increased liver copper concentrations
Pig/Hampshire and Yorkshire	NR/12	22.2	0 supplemental Cu	88	normal hemoglobin, hematocrit and liver copper levels
Pig/Hampshire and Yorkshire	NR/12	22.2	150 ppm diet supplement; 1.8 mg Cu^{+2}/kg/day	88	accelerated weight gain
Pig/Hampshire and Yorkshire	NR/12	22.2	200 ppm diet supplement; 2.5 mg Cu^{+2}/kg/day	88	accelerated weight gain
Pig/Hampshire and Yorkshire	NR/12	22.2	250 ppm diet supplement; 2.9 mg Cu^{+2}/kg/day	88	accelerated weight gain

*Source: Kline et al., 1971

NR = Not reported

appears that the increases in AST levels, jaundice and anemia principally reflected liver damage, since the postmortem examinations revealed gross hepatic degenerative changes, histologic centrilobular necrosis and bile canaliculi disruption, and there was no evidence of increased erythrocyte fragility. The addition of zinc or iron eliminated the jaundice and produced serum copper and AST concentrations similar to control levels after 4 weeks, but only supplemental iron afforded protection against the anemia.

In a second study (Suttle and Mills, 1966b), weanling female Large White pigs (6/group) were maintained on cornmeal diets that contained either soya-bean meal, dried skim milk or whitefish meal as protein supplements with 600 ppm basic copper carbonate for 48 days (6.4, 11.0 and 15.4 mg Cu^{2+}/kg/day, respectively). The soya-bean meal diet was similar to that used previously in the 750 ppm study (Suttle and Mills, 1966a). Results for control experiments (no supplemental copper) were not reported, but it was concluded that 600 ppm copper carbonate was only marginally toxic (causing slight growth depression and a temporary increase in serum copper, negligible effect on AST levels and gross evidence of toxicosis and jaundice in only 1 of the 6 pigs). The effect of the dried skim milk diet with 600 ppm copper carbonate on the pigs was also unremarkable, but the introduction of whitefish meal to the diet reportedly caused a moderately severe toxicosis (marked growth retardation, elevated serum Cu and AST levels, visible loss of condition and jaundice in 4 of the 6 pigs). The greater toxicity of the whitefish meal diet was attributed to a higher calcium level, which presumably adversely influenced zinc availability. Anemia developed gradually throughout exposure in pigs maintained on all the diets.

In a related experiment, 250 or 425 ppm of copper sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$) was added to the high calcium cornmeal whitefish diet and

fed to weanling female Large White pigs (6/group), creating optimal conditions for the development of copper toxicity (Suttle and Mills, 1966b). Administration of 425 ppm copper sulfate in the diet caused severe growth depression after 14 days, when "severe toxicosis" became evident; three pigs were slaughtered on the 47th day and another one on the 60th day to prevent unnecessary suffering. Autopsy revealed generalized jaundice, hypertrophy and cirrhosis of the liver, and GI hemorrhages. Food consumption and food conversion efficiency data were not provided for these animals; therefore, the daily intake of Cu^{2+} could not be estimated. When pigs were fed 250 ppm in the whitefish meal diet for 79 days (2.6 mg Cu^{2+}/kg/day), slight weight gain was noted over the first 30 days of treatment, but both serum AST and copper concentrations were significantly greater than control values at the 46th day, when three of the six pigs showed signs of jaundice. Concentrations of copper in the liver were significantly increased relative to unexposed controls after 79 days of treatment, but hemoglobin levels remained normal.

It is well recognized that sheep are especially sensitive to toxicity due to copper. Underwood (1977) described chronic copper toxicity in sheep grazing pastures in Australia in which the content of copper in soil and forages was abnormally high and/or forage levels of molybdenum were unusually low. Liver damage from grazing Heliotropium europaeum exacerbated the toxicity of high levels of copper. In ruminants, dietary levels of other trace elements, such as zinc, affect the toxicity of copper (NAS, 1977). Ruminants, however, are particularly unsuitable for use as a basis for human risk assessment, and further discussion of copper toxicity in these species will not be included in this document.

3.1.2. Inhalation. Pertinent data regarding the subchronic inhalation toxicity of copper in laboratory species could not be located in the available literature.

3.2. CHRONIC

Pertinent data regarding chronic exposure of laboratory animals to copper could not be located in the available literature. The most studied form of chronic copper toxicity in humans is Wilson's disease, or hepatolenticular degeneration (Williams, 1982). An inherited autosomal recessive disorder of copper metabolism, this disease is characterized by abnormally low plasma levels of ceruloplasmin, increased plasma copper levels and increased copper deposition in liver, brain, kidneys and cornea (Schroeder et al., 1966; Evans, 1973). Copper may accumulate in the liver of affected persons to a level ~20-fold that of unaffected individuals. This high level of hepatic copper destroys the hepatocytes, resulting in a release of copper into the general circulation. This released copper has many adverse effects including damage to erythrocytes, kidneys, corneas and the CNS (Scheinberg and Sternlieb, 1969). Symptoms include tremors to drooling, incoordination, seizures, behavioral abnormalities, anemia, jaundice and eventually death.

Another manifestation of chronic copper toxicity in man is the occurrence of "vineyard sprayer's lung" resulting from exposure to copper sulfate in Bordeaux mixture, used to control mildew in grapes (Pimental and Marques, 1969). Villar (1974) further described the symptoms of vineyard sprayer's disease in 14 male patients and 1 female patient with a prolonged history of intermittent (~3 months/year) exposure to Bordeaux mixture. Dyspnea, weakness, anorexia, weight loss, radiographic opacities and the presence of copper in the lungs were noted. Eventually the pulmonary opacities showed

regression followed by calcification. Later, Pimental and Menezes (1975) demonstrated copper-containing granulomas in vineyards sprayer's lung patients exposed for 3-15 years to Bordeaux mixture.

The occurrence of metal fume fever in workmen involved in polishing copper plates has been discussed in Section 3.1 (Gleason, 1968). Generally, air samples in the workplace contained 0.30-0.75 mg Cu/m³. A breathing zone air sample of the polishing wheel operator contained 0.120 mg Cu/m³. Installation of a ventilation system reduced copper levels in air to <0.008 mg/m³ and resulted in total abatement of symptoms.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Copper deficiency has been associated with neural degeneration, reduced growth, skeletal malformations and cardiovascular lesions in lambs, goats, rats, guinea pigs, dogs and chickens (Hurley and Keen, 1979). Ferm and Hanlon (1974) and DiCarlo (1980) showed conclusively that parenteral administration of solutions of copper sulfate or copper citrate produced terata in golden hamsters. Ferm and Hanlon (1974) demonstrated that the chelated (citrate) form was a far more potent teratogen than the inorganic (sulfate) form.

The teratogenicity of copper sulfate administered in the diets to two strains of mice was studied by Lecyk (1980). Groups of 7-22 DBA or C57Bl mice were given diets containing 0, 500, 1000, 1500, 2000, 3000 or 4000 ppm copper sulfate equivalent to added concentrations of 0, 199, 398, 597, 796, 1195 or 1593 ppm copper, respectively. Assuming that mice consume food equivalent to 13% of their body weight/day, these doses correspond to intakes of 0 (intrinsic copper content not specified for control group), 25.9, 51.7, 77.6, 103.5, 155.3 and 207.1 mg Cu/kg bw/day, respectively. Mice were treated from 30 days before mating until day 19 of gestation.

Low doses (500 and 1000 ppm) of copper sulfate stimulated embryonic development; increased litter size and fetal weight resulted. Higher doses increased fetal mortality, resulting in decreased litter size. Dietary levels of 3000 and 4000 ppm copper sulfate caused a low level of embryonic malformation, which was not observed in control mice or mice on lower dietary concentrations. In 55 living fetuses from C57Bl mice given 3000 ppm copper sulfate, 1 malformed fetus was noted with a defect in the lumbar vertebrae. Among 35 living fetuses from C57Bl mice given 4000 ppm copper sulfate, 3 abnormal fetuses were found: 1 with a hernia of the thoracic wall, 1 with hydrocephalus and 1 with rib and vertebral fusions. In 56 surviving fetuses from DBA mice given 3000 ppm copper sulfate, 2 abnormal fetuses were found, both with fusions of adjacent ribs. From DBA mice given 3000 ppm copper sulfate, 45 fetuses were found alive; 2 had encephaloceles and 2 had defects in their lumbar vertebrae. The incidence of terata appeared to be similar for both strains of mice tested. The levels of copper that resulted in formation of terata were considerably higher than those that resulted in toxic effects in pigs (Kline et al., 1971); hence, this study is not suitable for quantitative risk assessment.

No reports of terata in humans associated with oral exposure to copper have been located in the available literature.

3.3.2. Inhalation. No reports of terata in humans or animals resulting from inhalation exposure to copper or its compounds have been located in the available literature.

3.4. TOXICANT INTERACTIONS

Suttle and Mills (1966a,b) demonstrated an interaction of copper with both zinc and iron. Groups of six Large White female pigs were maintained

on diets containing 750 ppm of basic copper carbonate [$CuO_3 \cdot Cu(OH)_2 \cdot H_2O$] alone or with 500 ppm zinc carbonate or 750 ppm iron sulfate ($FeSO_4 \cdot 7H_2O$). Severe toxic effects (elevated serum copper and AST, jaundice, reduced hemoglobin, centrilobular liver necrosis and bile canaliculi disruption) were noted in control (copper carbonate fed) pigs, but the addition of either zinc carbonate or iron sulfate appeared to afford protection.

In ruminants, an antagonism between copper and molybdenum has long been recognized (Underwood, 1977). High levels of molybdenum in feedstuff may protect sheep exposed to high levels of copper or may precipitate copper deficiency in animals exposed to marginal levels of dietary copper. Excessive dietary levels of copper, particularly when combined with high levels of inorganic sulfate, have been shown to elevate the dietary requirement of selenium (Underwood, 1977).

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenicity of copper compounds in humans were not located in the available literature.

4.2. BIOASSAYS

Bionetics Research Labs (BRL, 1968) studied the carcinogenicity of copper hydroxyquinoline in $B6C3F_1$ and $B6AKF_1$ mice. Groups of 18 male and 18 female 7-day-old mice of both strains were given 1000 mg copper hydroxyquinoline in 0.5% gelatin by gavage until 28 days of age, at which time the compound was added to the basal diet (containing 5.7 ppm copper) at the rate of 2800 ppm (505.6 ppm copper). Animals were fed the treatment diet until 78 weeks of age, at which time they were killed. All mice killed or found dead were subjected to necropsy and histologic examination. Data were compared to those from positive, negative and vehicle control groups. No statistically significant increases in the incidence of lymphatic leukemias, reticulum cell sarcomas, pulmonary adenomas or carcinomas, hepatomas, hepatic carcinomas, mammary carcinomas, skin carcinomas or cancerous angiomas were observed in orally treated mice.

In the same study, groups of 18 male and 18 female 28-day-old $B6C3F_1$ and $B6AKF_1$ mice were maintained on the basal diet described above and given a single subcutaneous injection of 0.5% gelatin or 1000 mg copper hydroxyquinoline/kg bw in 0.5% gelatin (BRL, 1968). The animals were observed for 78 weeks, after which they were killed and subjected to examination as described previously for incidence of tumors. Treated male $B6C3F_1$ mice had a significantly ($p<0.001$) increased incidence of reticulum cell sarcomas (6/17), compared with controls (8/141). Male $B6AKF_1$ mice evidenced no tumor formation. Female treated and control $B6C3F_1$ mice had

incidences of 1/18 and 1/154 reticulum cell sarcomas, respectively. Female $B6AKF_1$ treated and control females had incidences of 3/18 and 5/157 reticulum cell sarcomas, respectively. Presumably, these incidences of reticulum cell sarcomas in female rats were not statistically significant.

In an earlier study, Gilman (1962) studied the carcinogenicity of cupric oxide, cupric sulfide and cuprous sulfide in 2-3-month-old Wistar rats. Groups of 30-32 rats were given single-dose bilateral injections of 20 mg cupric oxide (16 mg copper), cupric sulfide (13.3 mg copper) or cuprous sulfide (16 mg copper) into the thighs. Control groups were not mentioned. All groups were observed for up to 20 months, and survivors were subjected to histopathological examination. Surviving to termination were 10/32, 19/30 and 18/30 of the rats treated with cupric oxide, cupric sulfate and cuprous sulfate, respectively. No injection-site tumors were observed. Rats in the cupric oxide, cupric sulfate and cuprous sulfate groups had 0, 2 and 1 tumors, respectively. No further explanation of tumor types was available.

Haddow and Horning (1960) published bioassay results on various copper compounds (Table 4-1); no other experimental details were provided.

4.3. OTHER RELEVANT DATA

The available data from *in vitro* mutagenicity bioassays in microorganisms are not sufficient to allow a conclusion regarding the mutagenicity of copper. Demerec et al. (1951) reported positive results in an *Escherichia coli* reverse mutation assay with 2-10 ppm copper sulfate. Moriya et al. (1983) reported a lack of mutagenicity in *E. coli* and in *Salmonella typhimurium* strains TA98, TA1535, TA1537 and TA1538 with up to 5 mg copper quinolinolate/plate. This compound was mutagenic to *S. typhimurium* strain TA100, but only in the presence of a mammalian metabolic activation

TABLE 4-1

Tumorigenicity of Some Copper Compounds*

Agent Under Test	Number and Strain of Mice	Number of Weekly Subcutaneous Injections/Dose	Months of Experiment to Date and Survivors	Tumors Recorded
Copper-dextran	20 stock	6/0.1 cc of 1 in 4 dilution	10(13)	none
8-Hydroxyquinoline copper complex	20 stock	39/0.1 mg	10(14)	1 pleomorphic sarcoma
Cross-conjugated macrocycle copper porphyrin	20 stock	4/0.5 mg	10(14)	none
Copper phthalocyanine	20 stock	34/0.5 mg	8(17)	none
Copper phthalocyanine tetra-3-sulfonic acid	20 stock	36/0.5 mg	8(20)	none
Copper phthalocyanine tetra-4-sulfonic acid	20 stock	25/0.5 mg	8(11)	none

*Source: Haddow and Horning, 1960

system. Up to 5 mg of copper sulfate/plate failed to induce reverse mutations in S. typhimurium strains TA98 or TA100 either with or without metabolic activation (Moriya et al., 1983). Negative results with copper sulfate and copper chloride in Saccharomyces cerevisiae D-7 (Singh, 1983) and Bacillus subtilis (Nishioka, 1975; Matsui, 1980; Kanematsu et al., 1980) have also been reported.

Results from several isolated cell mutagenicity bioassays indicate mutagenic potential for some copper compounds. Errors in DNA synthesis have been induced in viruses (Sirover and Loeb, 1976), and chromosomal aberrations in rat hepatocytes have been induced by 15-20 mM cupric chloride or cupric acetate and 1.0 mM copper sulfate, respectively. Simian adenovirus cell transformation in Syrian hamster embryo cells was induced by 0.38 mM cupric sulfide and, to a lesser extent, with 0.08 mM copper sulfate (Casto et al., 1979). A positive recessive lethal response in D. melanogaster was observed to result from exposure of larvae or eggs to copper sulfate (Law, 1983).

4.4. WEIGHT OF EVIDENCE

Data regarding the carcinogenicity of copper were not sufficient to enable an IARC rating on the carcinogenicity of this element (U.S. EPA, 1983a). Cupric acetoarsenite was classified in 2A, but this was based on the weight of evidence for the arsenical moicty to react as arsenic trioxide, and was not related to the carcinogenicity of copper. Applying the criteria for evaluating the overall weight of evidence for carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), copper is most appropriately designated a Group D-Not Classified substance.

5. REGULATORY STANDARDS AND CRITERIA

Current regulatory standards and criteria for copper are shown in Table 5-1.

The ACGIH (1983) has set the TWA-TLV for copper fumes at 0.2 mg Cu/m^3 and the TLV for copper dusts and mists at 1 mg Cu/m^3 of air. Although Gleason (1968) reported symptoms of metal fume fever in workers exposed to 0.1 mg copper dust/m^3 air, the ACGIH felt that extensive industrial experiences with copper welding and refining experience in Great Britain supported the view that no ill effects result from exposure to fumes at concentrations up to 0.4 mg Cu/m^3.

The NAS (1977) has given 15 ppm copper in pig feed a GRAS categorization. Levels up to 200 ppm are often used in market hogs as a growth promoter.

The U.S. EPA (1980a), based on the organoleptic threshold of copper, has set the ambient water quality criterion for human effects at 1.0 mg/ℓ. U.S. EPA (1985) recommended this same level as the criterion for drinking water based on organoleptic criteria.

TABLE 5-1

Current Regulatory Standards and Criteria

Criteria	Value	References
TLV:fumes	0.2 mg/m³	ACGIH, 1980
TLV:dust	1.0 mg/m³	ACGIH, 1980
GRAS	15 ppm in pig feed	NAS, 1977
Ambient water quality criterion	1.0 mg/ℓ	U.S. EPA, 1980a
Daily recommended allowance for man	2-5 mg	NAS, 1980

6. RISK ASSESSMENT

Pertinent risk assessment data are summarized in the Appendix of this report.

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. Very few pertinent data were located in the available literature concerning the subchronic toxicity of orally administered copper. Howell (1959) studied the tissue distribution of copper in stock laboratory rats maintained for 16 months on diets containing 5000 ppm copper acetate (250 mg copper acetate or 80 mg Cu/kg bw/day). Both the liver and kidneys heavily accumulated copper. Since only one treatment level was used, and presumably no other criteria of toxicity were evaluated, this study was judged inadequate for use in deriving an MDT. Suttle and Mills (1966b) observed elevated serum AST activity and jaundice in pigs fed a diet containing 250 ppm copper sulfate (2.6 mg Cu^{2+}/kg/day). Although this level of copper is slightly less than that in the Kline et al. (1971) study (3.2 mg Cu/kg/day) in which no adverse effects were observed, it is inappropriate to use the dosage from the Suttle and Mills (1966b) study for derivation of an AIS because the diet was artificially altered to maximize the probability of copper toxicity. Kline et al. (1971) exposed groups of 12 pigs to dietary levels of 0, 150, 200 or 250 ppm copper sulfate for 88 days. In an earlier study, Kline et al. (1971) determined that 500 ppm dietary copper sulfate depressed the rate of weight gain. In these studies, therefore, 250 ppm dietary copper sulfate appeared to be a NOAEL. Assuming that a pig eats food equivalent to 5% of its body weight/day, this dietary level corresponds to a daily intake of 12.5 mg copper sulfate/kg bw, which, assuming 5 molecules of water of hydration, corresponds to 3.2 mg Cu/kg bw. For a 70 kg man, this exposure would be equivalent to 3.2 mg Cu/kg bw x

70 kg ÷ 100 = 2.2 mg Cu/man/day. Division by 100 represents an uncertainty factor of 10, introduced for interspecies extrapolation, and another uncertainty factor of 10 to afford greater protection for unusually sensitive populations. This estimate is essentially the same as the ADI of 2.6 mg/day estimated by the U.S. EPA (1985). It is suggested that the ADI of 2.6 mg/day be adopted here as the AIS (see Section 6.2.1. for the derivation of this number).

Patients suffering from G6PD deficiency may be at greater risk from excess levels of copper than the general population. Excessive copper has been shown to reduce the activity of the hexose monophosphate shunt, in which G6PD is apparently involved (Diess et al., 1970; Boulard et al., 1975; Calabrese et al., 1980). It has been reported that ~13% of the American Black male population has G6PD deficiency, and consequently may be at excessive risk from the toxic effects of copper. Individuals occupationally exposed to fine aerosols of copper or sprays containing copper sulfate (Pimental and Menezes, 1975) may be at additional risk, although it is not known what effect elevated oral intake of copper may have on this population.

The derived AIS in this report of 2.2 mg for humans is consistent with the recommendations of the NAS (1980) that an "adequate and safe" intake of 2-3 mg copper in a 70 kg man will satisfy the nutritional requirements and be protective of health. The Food and Drug Administration suggested that a 40-fold increase in the dietary requirement may represent a threshold for mild to severe chronic toxicity (U.S. EPA, 1985). It is also consistent with the drinking water standard of 1 mg/ℓ when water consumption is estimated at 2 ℓ/day (U.S. EPA, 1980a).

U.S. EPA (1983c) calculated a CS for copper, based on the elevated serum AST activity and jaundice observed by Suttle and Mills (1966b) in pigs fed a

diet containing copper sulfate that contributed 2.6 mg Cu^{2+}/kg bw/day for 79 days. Since this was a subchronic study, the animal MED was divided by 10 to convert to chronic exposure. The result was multiplied by the cube root of the ratio of the body weight of the pigs (33 kg) to that of an average man to derive a human MED of 0.20 mg/kg/day of Cu^{2+} or 14 mg/day for a 70 kg human. This MED corresponds to an RV_d of 3.8. The elevated serum AST activity and jaundice were assigned an RV_e of 5, since anemia was not observed. A CS of 19, the product of RV_d and RV_e, was calculated.

6.1.2. Inhalation. No satisfactory reports of subchronic inhalation exposure of laboratory animals to copper have been located in the available literature. Consequently, no subchronic maximum daily dose for inhalation exposure in man can be derived.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. Howell (1959) exposed rats to 5000 ppm dietary copper acetate for 16 months. By histochemical techniques, both the liver and kidneys were shown to "heavily accumulate" (U.S. EPA, 1985) copper. U.S. EPA (1985) calculated a daily intake in treated rats of 250 mg copper acetate/kg bw/day, corresponding to ~80 mg Cu/kg bw/day. This figure is ~25 times the level of copper (3.2 mg Cu/kg bw/day) to which pigs (Kline et al., 1971) were exposed in the study from which a reasonable subchronic oral acceptable intake was calculated. Since only one treatment level in rats was studied (Howell, 1959), and since copper was observed to "heavily accumulate" in the liver and kidneys, this study was judged unsatisfactory for determining an oral acceptable intake in man. Furthermore, a daily intake of ~6.4 mg Cu/kg bw/day for 61 days has been shown to reduce the rate of body weight gain in pigs (Kline et al., 1971), assuming that market pigs eat the equivalent of 5% of their body weight/day.

Frequently, when no suitable chronic studies are available from which to derive a maximum tolerable oral dose, the maximum tolerated subchronic oral dose is divided by an uncertainty factor of 10 to derive a maximum tolerated chronic oral dose. That rationale was considered and rejected for copper, because copper is an essential trace element in human nutrition, and the body ordinarily has homeostatic mechanisms to deal with reasonably moderate deficiencies or excesses. Furthermore, the animal based subchronic acceptable intake for oral exposure, 2.2 mg/man/day, is consistent with the recommended daily allowance proposed by the National Research Council (NAS, 1980). A recommended daily allowance (U.S. EPA, 1985) of 2-5 mg/day has been proposed by the National Research Council (NAS, 1980). This estimate is also in good agreement with U.S. EPA (1985). In that document an ADI of 2.6 mg/day was estimated based on a human LOAEL for acute GI symptoms of 5.3 mg/day (Chattani et al., 1965; Semple et al., 1960; Wyllie, 1957). An uncertainty factor of 2 was applied to this LOAEL due to a number of considerations including the transient nature of the effects and the essentiality of copper in human nutrition. It is proposed that the U.S. EPA (1985) ADI of 2.6 mg/day be adopted here as the oral AIC.

6.2.2. Inhalation. Pertinent data regarding chronic inhalation of copper in laboratory animals have not been located in the available literature. On the basis of extensive industrial experience with copper welding and metal refining operations in Great Britain, the ACGIH (1983) adopted a TLV of 0.2 mg/m^3 for fumes and 1.0 mg/m^3 for dusts and mists. Since these TLVs were based on extensive experience with industrial exposure, and since no animal toxicity studies were available, it was deemed prudent to use the TLVs as a starting point to derive a maximum tolerated chronic inhalation

dose. Assuming a man inhales 10 m^3 of air in a workday and works 5 days/week, the dose of copper vapor expected to be inhaled can be estimated to be 0.2 mg Cu/m^3 x 10 m^3 inhalation rate x 5/7 days/week = 1.4 mg copper vapors/day. Similarly, starting with a TLV of 1.0 mg copper dust or mist/m^3 of air, the dose is equivalent to 7.14 mg of copper dust or mist/day. An uncertainty factor of 10 is introduced to provide an additional safety factor for susceptible populations. Dividing the values for the dose by the uncertainty factor of 10 results in an AIC for chronic inhalation exposure of 0.14 mg copper vapors or fumes/day and 0.71 mg copper mists or dusts/day. The use of inhalation exposure levels expressed in units of mg/kg implicitly assumes that the exposure will be spread uniformly across the day.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. Bionetic Research Labs (BRL, 1968) studied the carcinogenicity of copper hydroxyquinoline in $B6C3F_1$ and $B6AKF_1$ mice. Dietary levels of 2800 ppm copper hydroxyquinoline (505.6 ppm copper, 25.3 mg Cu/kg bw) failed to produce tumors in mice after 77 weeks of exposure. In another part of this study, a single subcutaneous injection of 1000 mg copper hydroxyquinoline/kg bw was associated with a significantly ($p<0.001$) increased incidence of reticulum cell sarcomas in male $B6C3F_1$ mice. Male $B6AKF_1$ mice manifested no tumor formation, and treated female mice of both strains had no statistically significant incidence of tumor formation compared to controls. Mutagenicity bioassays do not clearly delineate a carcinogenic role of copper in the systems tested. Lack of sufficient data regarding carcinogenicity of copper in humans or in animal bioassays precluded derivations of health advisories on this basis.

6.3.2. Inhalation. The only evidence of human cancer related to inhalation exposure to copper was the suggestion by Pimental and Menezes (1975) that persons exposed to copper sulfate mist in Bordeaux mixture (vineyard sprayer's disease) may be at additional risk for the development of pulmonary alveolar cell carcinoma. No carcinogenicity bioassays involving inhalation exposure were found; hence, it was not possible to derive a q_1^* for inhalation exposure to copper.

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APPENDIX

Summary Table for Copper

	Species	Experimental Dose/ Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	NA	NA	NA	ND	NA
AIC	man	NA	NA	0.14 mg fumes/day 0.71 mg dusts/day	ACGIH, 1980
Oral					
AIS	man	5.3 mg/day	GI symptoms	2.6 mg/day	U.S. EPA, 1985
AIC	man	5.3 mg/day	GI symptoms	2.6 mg/day	U.S. EPA, 1985
Maximum composite score	pig	250 ppm copper sulfate in diet for 79 days (2.6 mg Cu^{2+}/kg/day (RV_d = 3.8)	elevated serum AST and jaundice (RV_e = 5)	19	Suttle and Mills, 1966b

NA = Not applicable

ND = Not derived